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Original Article

Colon targeted tablets of Albendazole with enhanced solubility by Complexation and Micellar Solubilization

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ABSTRACT: Albendazole (AZ) is a drug used for the treatment of gastrointestinal nematode infections. Phase solubility study was performed to investigate the optimized ratio of AZ: β-cyclodextrin (β-CD) solid dispersion (SD). Increase in the solubility of optimized AZ: β-CD SD was further enhanced by addition sodium lauryl sulfate (SLS) in different ratios was studied. Matrix tablets of the optimized ratio of AZ: β-CD SD with SLS and various proportions (10%, 15%, and 20%) of guar gum (GG). xanthan gum (XG) and pectin (PT) were prepared by non-aqueous wet granulation with PVP K30. Standard calibration curve for AZ was performed in three buffers like 0.1 N HCl, pH 6.8 phosphate buffer solution (PBS) and pH 7.4 PBS and absorbance were measured at 295 nm. Tablets were evaluated for various physical characteristics such as thickness, hardness, and drug content uniformity. The matrix tablets were subjected to *in vitro* drug release studies in 0.1 N HCl (2 h), pH 6.8 PBS (3 h) and pH 7.4 PBS (19 h) with and without rat caecal content medium. Formulation F9 shows 70.65% and 95.62% of AZ in with and without rat caecal content media respectively is selected as optimized one. Optimized formulation F9 passed the test for stability up to 3 months as per ICH guidelines.

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INTRODUCTION

Targeted drug delivery to the colon is very much attractive for local treatment of a spread of bowel diseases like (ulcerative inflammatory bowel disease, crohan's disease) protozoal infection, colonic cancer, and for local treatment of local colonic pathologies, and therefore protein and peptide drugs for the systemic delivery [1]. Oral route is most convenient and most popular route however alternative routes for CDDS may be used. The concentration of drug reaching the colon can rely on formulation factors the extent of retrograde spreading and therefore the retention time.

Formulations were done to prevent the acidic degradation of drugs by gastric HCl and so as to improve its bioavailability. Various polymers used for CTDD are pH dependent (Eudragit L100, Eudragit S100), enzyme dependent (Pectin, guar gum, xantham gum), and time dependent (HPMC K4M). Albendazole (AZ) is a broad spectrum anthelimentic. AZ, chemically known as methyl [5-(propylthio)-1H-benzimidazol-2-yl] carbamate, is used for the treatment of thread worm, hook worm and tape worm. It is an anthelmintic having a wide spectrum of activity [2-6]. Helimenthic infections are among the most common infections in the human beings, affecting a large population of the world's population [7].

The aim of the present work was to enhance the solubility of AZ by solid dispersion with β-CD and by micellar solubilization with SLS and to extend the release of drug up to 24 h by formulating matrix tablets with enzyme dependent polymers [pectin (PT), guar gum (GG) & xantham gum (XG)]. To target the delivery of solubility enhanced AZ at colon, for to increase its local action on the helimenthic parasites in the colon, and to aid for their better eradication.

MATERIALS AND METHODS

Materials: Albendazole was procured as a gift sample from A to Z pharmaceuticals, Chennai; β-cyclodextrin purchased from SD fine chemicals, Chennai; hydrochloric acid, guar gum & talc were purchased from Merck; potassium dihydrogen phosphate, xanthan gum, pectin, polyvinylpyrrolidone, microcrystalline cellulose & magnesium stearate were purchased from HI media; formic acid and sodium hydroxide were purchased from Fisher scientific.

Methods:

Standard calibration curve of AZ in three buffer solutions (pH 1.2 HCl, pH 6.8 & pH 7.4 phosphate buffers):

Preparation of pH 1.2 buffer (0.1N HCl): Solutions of any molarity xM may be prepared by diluting 85x mL of hydrochloric acid as per IP; 1996.

Preparation of pH 6.8 phosphate buffer: Place 50.0 mL of 0.2 M potassium dihydrogen phosphate in a 200 mL volumetric flask, add the 22.4 mL of 0.2 M sodium hydroxide and then add water to volume as per IP; 1996.

Preparation of pH 7.4 phosphate buffer (as per IP; 1996): Place 50.0 mL of 0.2 M potassium dihydrogen phosphate in a 200 mL volumetric flask, add the 39.0 mL of 0.2 M sodium hydroxide and then add water to volume.

Stock solution-I; (1 mg/mL (or) 1000 µg/mL): 50 mg of AZ was dissolved in 10 mL of formic acid and then volume was adjusted with the respective buffer up to the mark in a 50 mL volumetric flask and then placed in a sonicator for 5 min.

Stock solution-II; (10 µg/mL): 1 mL of the stock solution-I was taken into a 100 mL volumetric flask and then respective buffers were added up to the mark.

Working dilutions (5, 10, 15, and 20 µg/mL): 0.5, 1, 1.5, and 2 mL of the stock solution-II was taken into a 10 mL volumetric flask and then add respective buffers were added up to the mark, to obtain the series of working dilutions 5, 10, 15 and 20 µg/mL respectively.

The median conc. 10 µg/mL in all buffer solutions was scanned in the region of 200-400 nm with range of 1 nm for to determine the λ_{max} by using a double beam UV-Vis spectrophotometer (Agilent technologies cary-60) to determined λ_{max} for AZ in different buffers. The standard calibration curve was plotted by taking conc. (µg/mL) on X-axis and absorbance at λ_{max} on Y-axis.

Table 1: Formulation table of AZCTs

Drug- excipient compatibility studies: FTIR spectra of AZ and AZ: polymer (1:1) physical mixtures were recorded out, in the region of 400-4000 cm^{-1} at spectral resolution of 2 cm^{-1}, by the direct sampling method with isopropyl alcohol as solvent, using FTIR instrument (Agilent technologies Cary 630 FT-IR, Japan).

Phase solubility studies: Phase solubility studies were performed according to the method of Higuchi and Connors [8]. An excess amount of AZ (1 g) was added to 50 mL of pH 7.4 PBS containing various concentrations of β-CD (2-20 mM). The flasks were shaken continuously at 30 °C for 3 days to reach equilibrium. About 3 mL of sample was withdrawn and filtered through a 0.45 µm nylon membrane filter. Filtrate was diluted appropriately and assayed at 295 nm (Agilent technologies cary-60). The slope of the best fit line of the phase solubility diagram was calculated. The stability constant (K_s) was determined from that slope by the following equation.

$$K_s = \frac{Slope}{S0\,(1-Slope)} \qquad \textit{Eq. No. (1)}$$

Preparation of solid dispersion (SD): Accurate weighed quantities of AZ and β-CD in different ratios (1:1, 1:2 and 1:3) are added to 20 mL of methanol in a beaker, the dispersion was mixed with the help of magnetic stirrer until a smooth paste was obtained and the solvent was evaporated at 60 °C. The dried SD was triturated and passed through sieve number #60 ASTM.

Optimization of AZ: β-CD ratio: Solubility studies of AZ: β-CD SD (1:1; 1:2 and 1:3) was performed in 50 mL of pH 7.4 PBS for to optimize the AZ: β-CD ratio.

Optimization of AZ: SLS ratio: Solubility studies with optimized ratio of AZ: β-CD SD (1:2) was performed with varying ratios of AZ: SLS (1:0.1, 1:0.2 and 1:0.3) in 50 mL of pH 7.4 PBS for to optimize the AZ: SLS ratio.

In both the cases the flasks were shaken continuously at 30 °C for 3 days to reach equilibrium. About 5 mL of sample was withdrawn and filtered through a 0.45 µm nylon membrane filter, diluted if necessary and assayed by using UV-Visible spectrophotometer (Agilent technologies cary-60) at 295 nm.

Formulation of AZCTs: Weighed accurate quantities of SD, SLS, and gum [PT/ GG/ XG], triturated it in a mortar with a pestle for 5 min. 5% w/v PVP alcoholic solution was added to obtain wet mass. The wet mass is passed through sieve number #20 ASTM to get wet granules, which are dried in a hot air oven at 60ºC for 1 h. Dried granules were passed through sieve number #40 ASTM. Finally lubricated with added sieve number #44 ASTM passed talc and magnesium stearate by mixing in a poly bag 5 min. Tablets were compressed with a avg. wt. of 600 mg and avg. hardness of 6 kg/cm^2. Formulation table of AZCTs was given in table 1.

Pre-compression studies: The non-aqueous wet granulated blends of AZCTs were evaluated for their flow and compression properties [9].

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
	10% PT	15% PT	20% PT	10% XG	15% XG	20% XG	10% GG	15% GG	20% GG
ABZ: β-CD (1:1)	400	400	400	400	400	400	400	400	400
SLS	20	20	20	20	20	20	20	20	20
Pectin	60	90	120	--	--	--	--	--	--
Xanthan gum	--	--	--	60	90	120	--	--	--
Guar gum	--	--	--	--	--	--	60	90	120
MCC	48	48	48	48	48	48	48	48	48
Mg. Stearate	6	6	6	6	6	6	6	6	6
Talc	6	6	6	6	6	6	6	6	6
Total	**600**	**600**	**600**	**600**	**600**	**600**	**600**	**600**	**600**

Angle of Repose (AR): Was determined by funneling method, the blend was poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2 cm above hard surface. The blend was poured till the time when the upper tip of the pile surface touched the lower tip of the funnel. The θ is calculated by the equation.

$$AR \text{ or } \theta = \tan^{-1} h/r \qquad \textit{Eq. No. (1)}$$

Where, θ = angle of repose, h = height of the heap and r = radius of base of heap circle.

Bulk density (BD): A quantity of 2 gm of SLT blend from each formulation, previously lightly shaken to break any agglomerates formed, was introduced into a 10 mL measuring cylinder and the volume is noted as bulk volume. The BD was calculated by the equation.

$$BD = \text{wt. of blend} / \text{Bulk volume} \qquad \textit{Eq. No. (2)}$$

Tapped density (TD): After the determination of BD, the measuring cylinder was fitted to a tapped density apparatus. The tapped volume was measured by tapping the powder for 500 times. Later the tapping was done for another 750 times and the tapped volume was noted (the difference between these two volumes should be less than 2%). If it is more than 2%, tapping is continued for another 1250 times and the constant tapped volume was noted. The TD was calculated by the equation.

$$TD = \text{Wt. of blend} / \text{Tapped volume} \qquad \textit{Eq. No. (3)}$$

Carr's Index (CI): The percentage of CI is calculated by the equation.

$$CI = (TD-BD) \times 100/TD \qquad \textit{Eq. No. (4)}$$

Hausner's Ratio (HR): Is a number that correlates to the flow ability of a powder. It is calculated by the equation.

$$HR = TD/BD \qquad \textit{Eq. No. (5)}$$

Post-compression studies [10, 11]:

Avg. wt.: An electronic balance (Mettler Toledo, 3- MS-S / MS-L, Japan) was used to accurately weigh the individual wt. of 20 tablets (n=20) which were randomly selected from each formulation and checked for the acceptability of wt. variation.

Hardness: To evaluate the diametrical crushing strength, 3 tablets (n=3) from each formulation were tested using a hardness tester (Monsanto type hardness tester, MHT-20, Campbell Electronics, India).

Thickness: Thickness of 3 tablets (n=3) from each formulation was determined using a Vernier caliper (Mitutoyo Corporation, Japan).

Friability: The friability of the 10 tablets from each batch (n=1) was tested by a friabilator (SINGLA, TAR 120, Germany) at a speed of 25 rpm for 4 min. The tablets were then dedusted, reweighed, and percentage weight loss was calculated by the equation,

$$\%\ Friability = (\text{Initial Wt.} - \text{Wt. after friability}) \times 100 / \text{Initial Wt.} \qquad \textit{Eq. No. (6)}$$

Swelling index (%SI): Three tablets (n=3) whose weight was predetermined were placed in each dissolution flask containing 900 mL of pH 7.4 PBS at 37°C ± 0.5°C and the apparatus was run at 100 rpm using paddle. The tablets were taken out after completion of the 3rd h and weighed after the excess of water at the surface had been removed with filter paper. The increase of the weight on the tablet reflects the swelling of tablet after water uptake. It was estimated according to following equation.

$$\%SI = 100 (W_w - W_i) / W_w \qquad \textit{Eq. No. (7)}$$

Where, W_w and W_i were the weights of the tablet after and before swelling.

Drug content: The matrix tablets were tested for their drug content following crushing and powdering three tablets (n=3) from each batch separately. The amount of powder equivalent to 100 mg of the drug was weighed and dissolved in 100 mL of pH 7.4 PBS (1000 µg/mL). After 5 min of ultrasonication and filtration through a 0.45 µm nylon membrane, aliquots of 1 mL were taken from this solution and diluted to 100 mL with pH 6.8 PBS (10 µg/mL). The absorbance of resulting solutions was measured in a UV-Vis spectrophotometer at 295 nm.

Preparation of 4 % w/v rat caecal content medium (RCCM): The protocol (SVCP/IAEC/I-006/2017-18 dated on 15/12/2018) for animal studies was approved by the Institutional Animal Ethics Committee (IAEC) of Sree Vidyanikethan College of Pharmacy, Tirupati and is in accordance with guidance of committee for the purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Social Justice and Empowerment, Govt.

of India. Male albino rats weighing 150 to 200 g were kept on a normal diet and administered 1 mL of 1% w/v solution of the selected gums (GG, XG & PT) in water. This treatment was continued for 7 days to induce the specific enzyme responsible for degradation of selected gums *in vivo*. 30 min before the dissolution studies began, the anesthetized rats were sacrificed, the rat abdomen was opened, ligatures were made before and after the caecum and the caecum was removed under anaerobic conditions. The caecum bag was opened and its contents were weighed and homogenized, then suspended in pH 7.4 PBS to give the 4 % w/v conc. of caecal contents. The suspension was centrifuged at 2000 rpm for 10 min at 4ºC to disrupt the bacterial cells followed by sonication. The resultant mixture was centrifuged at 2000 rpm for further 20 min. As the environment of caecum is anaerobic, all operations were performed in a CO_2 atmosphere [12].

In vitro dissolution studies (without and with RCCM): *In vitro* drug release studies of AZCTs were carried out using a USP type I dissolution test apparatus (paddle, 100 rpm, 37 ± 0.5°C) in 900 mL of dissolution medium (pH 1.2 HCl buffer for first 2 h, pH 6.8 PBS for next 3 h and pH 7.4 PBS without or with 4 % w/v rat caecal content for next 19 h). At predetermined intervals, 5 mL of samples were withdrawn through a 0.45 µm nylon filter discs, by replacing with the same amount of fresh respective medium and after suitable dilution they were assayed spectrophotometrically at 295 nm [13, 14].

In vitro drug release kinetic studies (without and with RCCM)): The *in vitro* drug release data of all batches were fitted into zero order, first order, Higuchi and Korsemeyer- Peppas models to ascertain the drug release kinetics. The drug release from the matrix tablets whether depends on drug's concentration or not was explained by zero and first order [15]. Higuchi model describes whether the drug release is predominantly by diffusion or not. The Korsemeyer- Peppas model further explains the mechanism of diffusion [16, 17]. The respective models were defined by the equations below.

Zero order: $Q_t = Q_0 + K_0 t$ ***Eq. No. (8)***

First order: $\log Q = \log Q_0 - K_1 t / 2.303$ ***Eq. No. (9)***

Higuchi model: $Q_t = K_H t^{1/2}$ ***Eq. No. (10)***

Korsemeyer-Peppas model: $M_t / M_\infty = K t^n$ ***Eq. No. (11)***

Where Q_t is the amount of drug dissolved at time, t; Q_0 is the initial amount of drug in the solution at time $t=0$, Q is the amount of drug remaining at time, t; M_t/M_∞ is the fraction of drug released at time, t and n is diffusion exponent. K_0, K_1, K_H and K refer to the rate constants of respective kinetic models.

Accelerated stability studies: Stability studies of the optimized AZCT; F9, packed in 10 CC HDPE containers up to 3 months were carried according to International Conference on Harmonization (ICH) guidelines; in a humidity chamber (NSW-175, Narang Scientific work, India) maintained at 45°C ± 2°C and 75% ± 5% RH [18].

At the end of every month up to 3 months, the samples were withdrawn and evaluated for post compression studies.

RESULTS AND DISCUSSION

Drug-excipient compatibility studies: The FTIR spectrum of AZ showed N-H stretching vibration at 3336 cm^{-1} due to carbamate, bending vibration at 1525-1630 cm^{-1} and aliphatic C-H at 2958 cm^{-1}, stretching of alkane at 2959 cm^{-1}, coo bending of ketone at 1710 cm^{-1}. The IR bands of AZ, AZ+β-CD and AZ+polymer(s) (1:1 ratio physical mixtures) show no significant shifts or reduction in intensity of the FTIR bands [19]. Hence, there was no incompatibility between the AZ, β-CD and polymers used in the study. The comparative FTIR spectra of AZ, AZ+β-CD and AZ+polymer(s) (1:1 ratio physical mixtures) were shown in (Fig. 1).

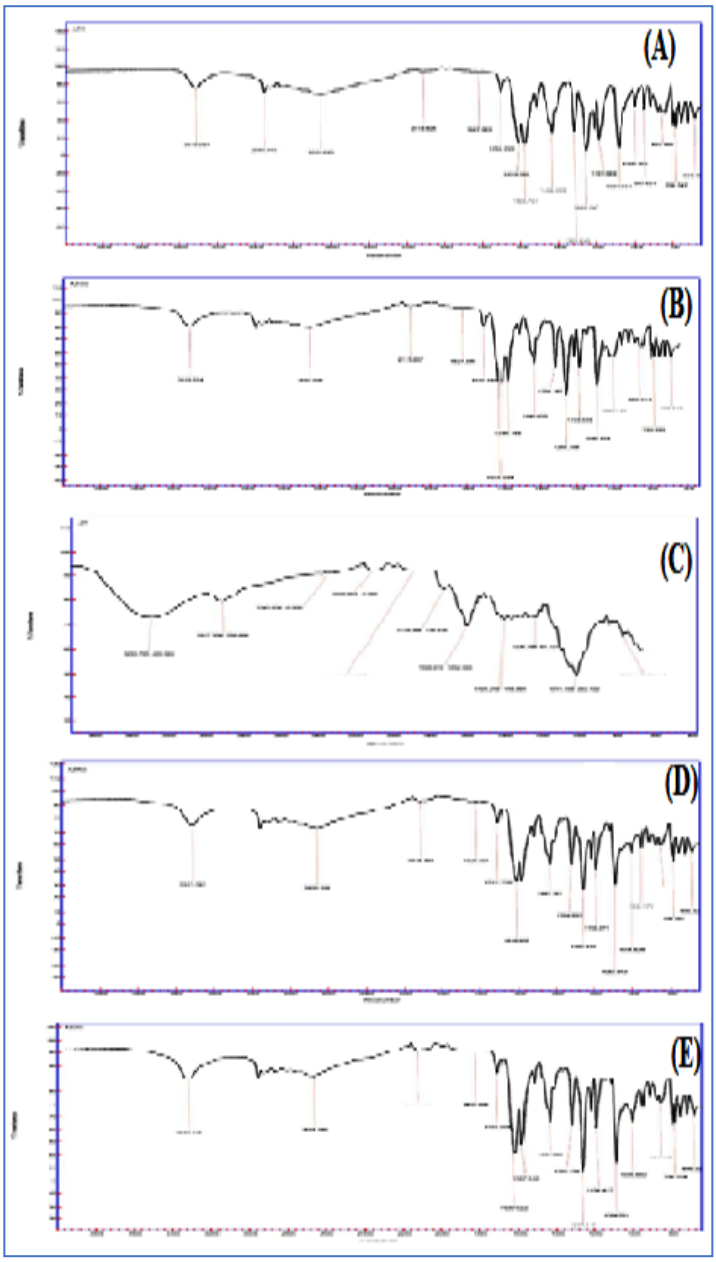


Fig.1. FTIR spectrum of (A) AZ; (B) AZ+β-CD (C) AZ+PT; (D) AZ+ XG; and (E) AZ+GG

Standard calibration curve: In three buffer solutions (pH 1.2 HCl, pH 6.8 and pH 7.4 PBS) the standard curve is showing linearity

with a regression coefficient (r^2 = 0.999) and obeys Beer's law in the concentration range of 0-20 µg/mL.

Phase solubility studies: Indicates the solubility of AZ increased proportionally with an increase in the conc. of β-CD. Solubility is increased with AZ: β-CD ratio 1:1 to 1:3; as the increase in 1:3 ratio is not significant when compared to 1:2 ratio [20]. Further solubility studies in optimizing the conc. of SLS is carried with 1:2 ratio. The optimized AZ: β-CD: SLS Ratio is 1:2:0.2 respectively. Solubility data of AZ and AZ: β-CD: SLS was tabulated in (Table 2). Phase solubility diagram of AZ with β-CD in pH 7.4 PBS was shown in (Fig. 2).

Pre-compression studies: The angle of repose of all the directly compressible blends of AZCTs are ranging between 20°.08'±1.98 to 23°.02'±0.39, CI and HR were found to be in the range of 11.53 to 16.25% and 1.13 to 1.19 respectively, indicating excellent flow properties and compressibility of the blends. Results of pre-compression studies of AZCTs are tabulated in (Table 3).

Post-compression studies: As the % wt variation of all batches is within ±5% w/w (Acceptable limit for tablets with avg. wt. more than 324mg), they passed the wt. variation test as per United States Pharmacopoeia-30, National Formulary-25 (USP 30-NF 25). The thickness of tablets was found to be between 6.21±0.05 to 6.28±0.05 mm. The hardness of tablets was found to be between 6.01±0.37 to 6.24±0.17 kg/cm^2, indicating satisfactory mechanical strength. The % friability was NMT 1.0% w/w for all the formulations, which is an indication of good mechanical resistance to physical erosion of the tablet.

As the % assay of all batches is within 96.50±0.84 to 99.60±0.85% (Acceptable limit of ±5%), they passed the content uniformity test as per USP26 & NF21. Results of post-compression studies of AZCTs are tabulated in (Table 4).

Table 2: Solubility data of AZ and AZ: βCD: SLS

AZ: β-CD: SLS Ratio	Solubility (mg/mL)	Folds of increase in solubility
1:0:0	0.0012	--
1:1:0	0.0047	3.91
1:2:0	**0.0641**	**53.4**
1:3:0	0.0642	53.5
1:2:0.1	0.1456	121.3
1:2:0.2	**0.1745**	**145.4**
1:2:0.3	0.1747	145.5

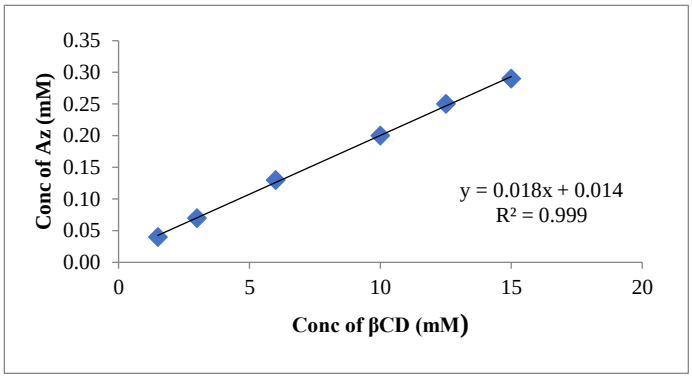


Fig. 2: Phase solubility diagram of AZ with β-CD in pH 7.4 PBS

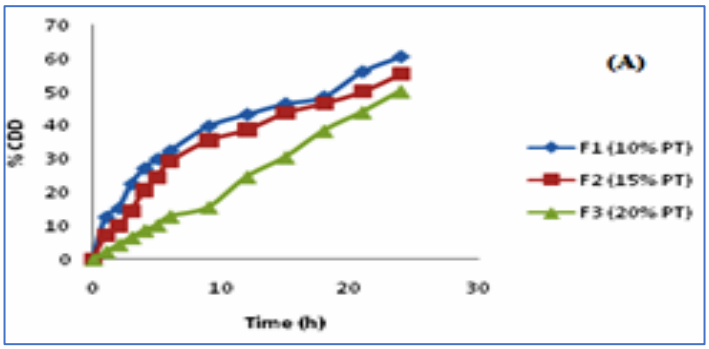
Table 3: Results of pre-compression studies of AZCTs

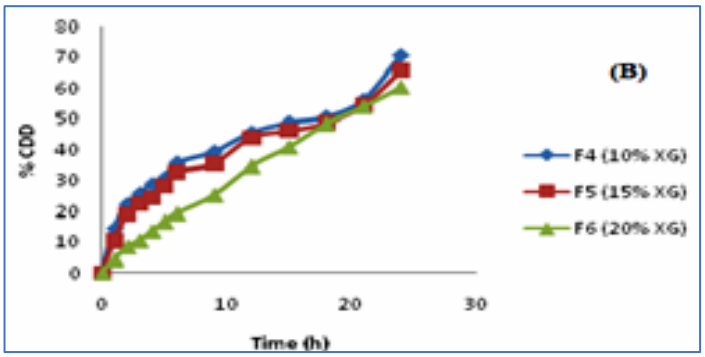
F. Code	AR (º) (n=3)	BD (g/ cm^3) (n=3)	TD (g/ cm^3) (n=3)	HR*( ) (n=3)	CI* (%) (n=3)
F1	22.06±0.76	0.583±0.01	0.674±0.06	1.15	13.50
F2	22.24±0.35	0.598±0.01	0.676±0.04	1.13	11.53
F3	21.38±0.62	0.589±0.02	0.689±0.01	1.16	14.50
F4	23.02±0.39	0.590±0.01	0.698±0.02	1.18	15.47
F5	22.36±0.51	0.584±0.03	0.693±0.07	1.18	15.72
F6	21.46±0.44	0.583±0.01	0.668±0.02	1.14	12.72
F7	22.12±0.58	0.571±0.02	0.670±0.04	1.17	14.77
F8	21.78±0.28	0.582±0.01	0.695±0.05	1.19	16.25
F9	**20.08±1.98**	**0.586±0.03**	**0.694±0.01**	**1.18**	**15.56**

Table.4. Results of post-compression of AZCTs

F. Code	Avg. wt. (mg) (n=20)	Thickness (mm) (n=3)	Hardness (kg/cm^2) (n=3)	Friability* (%) (n=1)	SI at 3rd h (%) (n=3)	% Assay (%) (n=3)
F1	600.11±3.41	6.26±0.07	6.01±0.37	0.4	25.12±1.89	97.84±0.90
F2	601.21±3.59	6.28±0.05	6.08±0.29	0.6	26.04±1.24	98.40±0.04
F3	596.02±1.10	6.23±0.04	6.02±0.21	0.5	29.23±1.12	98.80±0.92
F4	599.11±2.18	6.21±0.05	6.22±0.26	0.3	30.15±0.98	97.70±0.18
F5	599.51±2.67	6.25±0.03	6.24±0.17	0.4	29.13±1.16	96.50±0.84
F6	597.03±0.92	6.24±0.04	6.21±0.21	0.2	32.32±1.25	99.01±0.86
F7	599.71±1.98	6.22±0.04	6.16±0.32	0.1	31.05±0.99	97.12±0.23
F8	601.12±1.56	6.27±0.02	6.10±0.26	0.2	33.03±0.86	96.98±0.36
F9	**598.03±1.11**	**6.22±0.04**	**6.18±0.21**	**0.2**	**35.12±0.99**	**99.60±0.85**

***In vitro* dissolution studies (without and with RCCM):** As the conc. of polymer (GG/XG/PT) increases, there is an increased viscosity of the gel matrix and decrease in the effective diffusion coefficient of the AZ [21]. Other factors that may contribute to differences in drug release profiles include; differences in water penetration rate, water absorption capacity, polymer swelling and drug: polymer ratio [22, 23]. Among all factors, drug: polymer ratio is important factor affecting the rate of drug release from the matrix, which has to be optimized [24]. All the formulations with various conc. of polymer (GG/XG/PT) are able to extended MZ release up to 24 h in dissolution without RCCM. Among all, the batches with highest conc. (20%w/w) of polymers (GG/XG/PT) extends the release of AZ up to 24 h with a better zero order release profile (r^2 =0.999), hence they are selected to perform the dissolution with RCCM, for to simulate the colonic environment. *In vitro* dissolution profiles of AZCTs without RCCM are shown in (Fig. 3). *In vitro* dissolution profiles of selected (F3, F6 & F9) AZCTs with RCCM are shown in (Fig. 4).





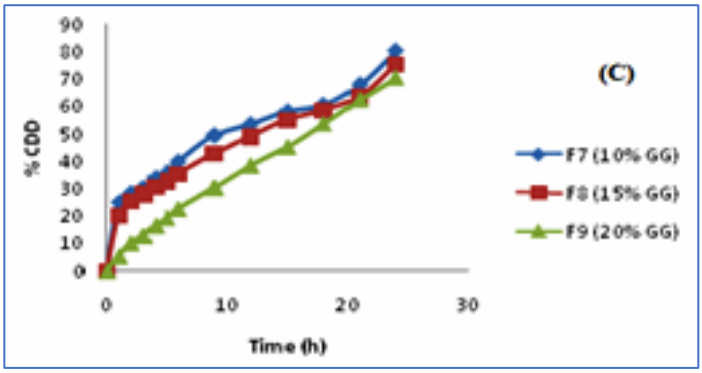


Fig. 3: *In vitro* dissolution profiles of AZCTs without rat caecal content medium; (A) PT; (B) XG and (C) GG

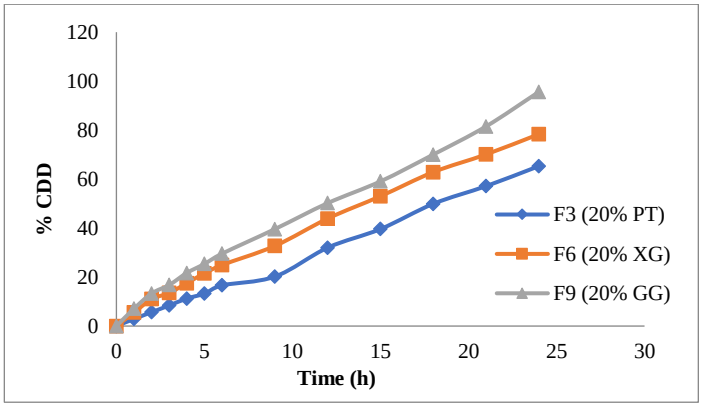


Fig. 4: *In vitro* dissolution profiles of selected (F3, F6 & F9) AZCTs with rat caecal content medium

***Drug release kinetics (without and with RCCM)*:** Among all the batches, AZCT; F9 (20% w/w GG), drug release kinetics fitted best to the zero order (as zero order, r^2=0.995 without & with RCCM), indicating the drug release from the matrix does not depends on drug's conc. Drug release process is predominantly by diffusion when Higuchi's, $r^2 > 0.9$ (r^2=0.957 without RCCM & r^2=0.951 with RCCM); and the mechanism of diffusion is by non-Fickian when Korsemeyer-Peppa's diffusion coefficient (n) is $0.45 < n < 0.89$ for cylindrical shape, (n=0.787 without RCCM & n=0.771 with RCCM). Results of *in vitro* drug release kinetics of AZCTs without and with RCCM were tabulated in (Table 5).

Table 5: Results of *in vitro* drug release kinetics of AZCTs without and with rat caecal content medium

F. Code	Without rat caecal content					With rat caecal content				
	Zero order	First order	Higuchi	Krosmeyer-Peppas		Zero order	First order	Higuchi	Krosmeyer-Peppas	
	r^2	r^2	r^2	r^2	n	r^2	r^2	r^2	r^2	n
F1	0.896	0.954	0.988	0.981	0.492	--	--	--	--	--
F2	0.919	0.964	0.984	0.972	0.654	--	--	--	--	--
F3	**0.996**	**0.985**	**0.916**	**0.996**	**0.975**	**0.996**	**0.974**	**0.916**	**0.995**	**0.969**
F4	0.896	0.926	0.973	0.982	0.440	--	--	--	--	--
F5	0.921	0.952	0.983	0.979	0.512	--	--	--	--	--
F6	**0.995**	**0.995**	**0.957**	**0.998**	**0.825**	**0.995**	**0.980**	**0.956**	**0.997**	**0.822**
F7	0.895	0.937	0.974	0.960	0.365	--	--	--	--	--
F8	0.919	0.958	0.984	0.977	0.403	--	--	--	--	--
F9	**0.995**	**0.982**	**0.957**	**0.998**	**0.787**	**0.995**	**0.840**	**0.951**	**0.998**	**0.771**

Accelerated stability studies: As there were no significant differences in post compression studies (wt. variation, thickness, hardness, friability and *in vitro* dissolution studies) of initial & accelerated stability samples of optimized AZCT; F9 up to 3 months in the 10 cc HDPE pack, it passes the test for stability as per ICH guidelines. Results of accelerated stability studies of optimized AZCT; F9 were tabulated in (Table 6). Comparative *in vitro* dissolution profiles of initial and accelerated stability samples of optimized AZCT; F9 were shown in (Fig.5) reveals there was no significant change. Comparative FTIR spectra of AZ (pure drug) and accelerated stability samples of optimized AZCT were shown in (Fig.6) reveals there is no significant change in the functional groups of the AZ due to interaction with polymers and other excipients used in the formulation.

Table 6: Results of accelerated stability studies of optimized AZCT; F9

Time (Month)	Avg. wt. (mg)	Thickness (mm)	Hardness (kg/cm^2)	% Friability (%)	SI at 3rd h (%)	% Assay (%)
1M	598±1.11	6.22±0.044	6.18±0.213	0.2	35±0.39	99.6±0.85
2M	597±0.95	6.09±0.19	5.99±0.98	0.2	33±0.15	98.01±0.16
3M	596±0.09	5.81±1.27	5.63±0.15	0.15	30±0.09	97.23±0.34

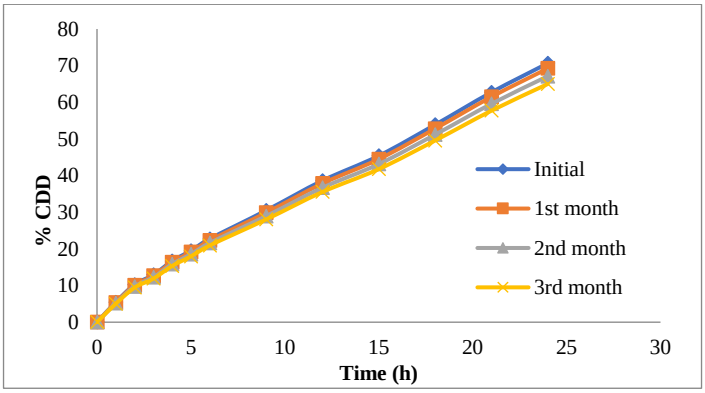


Fig. 5: *In vitro* dissolution profiles of accelerated stability samples of optimized AZCT; F9

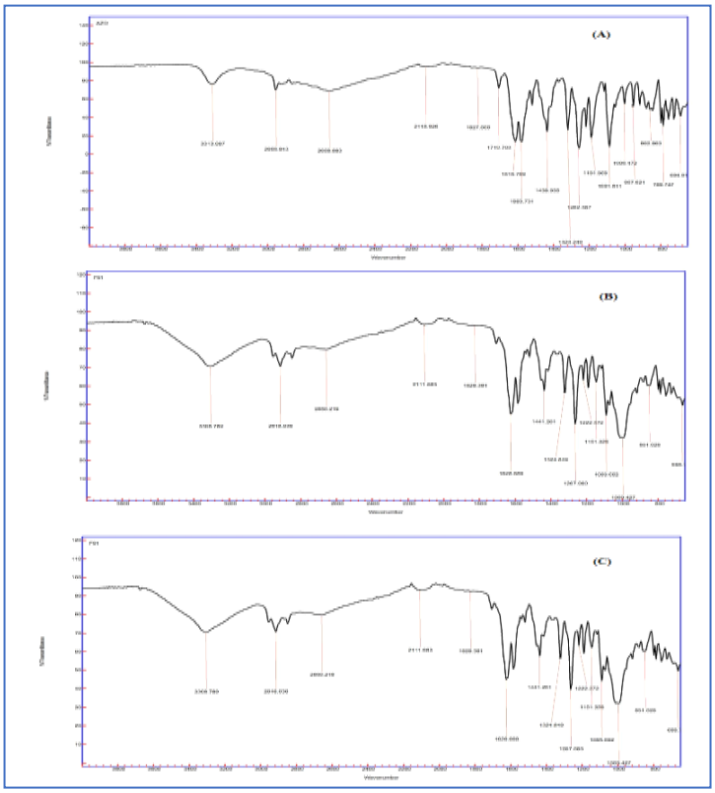


Fig. 6: Comparative FT-IR spectra of (A) AZ (pure drug); (B) Initial; and (C) 3M- accelerated stability sample of optimized AZCT; F9

CONCLUSION: The prepared AZCTs pass the pre and post compression studies. All the formulations with various conc. of polymer (GG/XG/PT) are able to extended MZ release up to 24 h in dissolution without RCCM. Among all, the batches with highest conc. (20%w/w) of polymers (GG/XG/PT) extends the release of AZ up to 24 h with a better zero order release profile (r^2 =0.999), hence they are selected to perform the dissolution with RCCM, for to simulate the colonic environment. Among all the batches, AZCT; F9 (20% w/w GG), drug release kinetics fitted best to the zero order is selected as optimized one. Optimized formulation, AZCT; F9 pass the test for stability as per ICH guidelines. The solubility of AZ was enhanced by solid dispersion with β-CD and micellar solubilization with SLS and the release of drug was extended up to 24 h by formulating matrix tablets with enzyme dependent polymer guar gum. Colon targeting of solubility enhanced AZ will increase its local action on the helminthic parasites in the colon, and aids for their better eradication.

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